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Case Report

Psychophysiological Differences in Identical Twins Discordant for Schizophrenia: A Critical Index for the Onset of Schizophrenia

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Department of Health and Welfare Science, Sendai College, Shibata, Japan,
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YOSHIDA, S., NUMACHI, Y., FUKUSHIMA, S., MATSUMOTO, K., YAMAZAKI, H., OSAKABE, K. and MATSUOKA, H. *Psychophysiological Differences in Identical Twins Discordant for Schizophrenia: A Critical Index for the Onset of Schizophrenia*. Tohoku J. Exp. Med., 2006, **209** (2), 159-162 —— It has been hypothesized that not only genetic but also environmental factors contribute to the onset of schizophrenia. We therefore conducted psychophysiological studies on a pair of identical twins discordant for schizophrenia, to differentiate non-genetic from genetic indexes possibly associated with this disease. The affected and unaffected twins were 28 year-old females. The affected twin was diagnosed as having schizophrenia based on the Diagnosis and Statistical Manual of Mental Disorders, third edition revised (DMS-III-R), whereas the unaffected twin had no psychiatric disorders. The brain potentials evoked by visual stimulation (visual event-related potential [visual ERP]) were recorded. The components of the visual ERP, which are believed to reflect pattern cognition, semantic processing and the failure to use preceding word information, were compared with normal subjects. Both twins showed abnormal semantic processing and similar failure to use preceding word information. Abnormality of semantic processing was marked in the affected twin. These results indicate that failure to use preceding word information might reflect only genetic factors, whereas abnormal semantic processing might reflect both genetic and non-genetic factors because the affected twin was considered to show accelerated deterioration after the disease onset. However, only the affected twin showed abnormal pattern cognition, which might be attributable to non-genetic factors such as an acquired vulnerability to schizophrenia. We suggest that the impairment of pattern cognition evaluated by visual ERP may be a critical index for the onset of schizophrenia. ———— acquired vulnerability; visual event related potential; discordant identical twins; schizophrenia

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Monozygotic (MZ) twins show concordance rates for schizophrenia of approximately 50% (McGuffin et al. 1994). A rate of 100% would be expected on the basis of genetic equivalence alone. Thus, 50% concordance rates for schizophrenia in MZ twins indicate not only genetic but also environmental factors to play important roles in the development of this disease. Many biological indicators have been proposed to confer vulnerability to schizophrenia development. However, differentiating indicators representing acquired vulnerability from those conferring genetic vulnerability remains difficult. MZ twins discordant for schizophrenia reportedly exhibit much lower within-pair electroencephalographic (EEG) concordance than healthy MZ twins. These results prompted us to hypothesize that EEG abnormalities associated with schizophrenia reflect non-genetic, pathological developments affecting genetically identical brains (Stassen et al. 1996). However, this hypothesis was not confirmed. On the other hand, though schizophrenics showed reduced P3 amplitude, a cognitive component of brain potentials evoked by events (event-related potential [ERP]), it was not possible to identify whether this abnormality is environmental or genetic in origin (Anokhin et al. 2001). In 1999, we reported delayed NA latency, one of the ERPs evoked by visual stimulation (visual ERP), to be a reliable index of vulnerability to relapse in schizophrenics in remission (Matsuoka et al. 1999a). We also reported schizophrenics to lack a repetition priming effect, based on the N400 component of the visual ERP (Matsuoka et al. 1999b). However, whether NA and N400 reflect genetic or acquired vulnerability remains unclear. We describe herein female identical twins discordant for schizophrenia, in whom we attempted to differentiate non-genetic from genetic indexes for the onset for schizophrenia in terms of ERPs.

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The subjects were 28 year-old female twins. Their physical and mental developments had been essentially the same through adolescence. They had very similar academic records in high school. After graduating from the same high school, they were employed as office workers at different companies. The affected and unaffected twins married at ages 21 and 27 years, respectively. The affected twin gave birth to a child at the age of 25. When the affected twin was 28 years old, she was admitted to our hospital for six months because of a religious persecution delusion which involved her "helping the world," auditory hallucinations and flight of ideas which had initially manifested at the age of 27. She was diagnosed as having schizophrenia (paranoid type) in accordance with the Diagnosis and Statistical Manual of Mental Disorders, third edition revised (DMS-III-R, American Psychiatric Association 1987) and was medicated with haloperidol (9 mg/day). The unaffected twin had been working and had no psychiatric disorders.

Examinations were carried out for both twins during essentially the same time period while the affected twin was in remission during her hospitalization. In conducting this study, we followed the guidelines of the ethics committee of Tohoku University. After a thorough description of our study to the subjects, written informed consent was obtained from both.

Visual NA and N400 potentials (Matsuoka et al. 1999a, 1999b) were used to assess both twins. The word set consisted of two meaningful kana (Japanese phonograms) ($p = 0.3$), two pronounceable but meaningless kana ($p = 0.3$), and unpronounceable foreign letters. In the repetition set, the non-targets consisted of meaningful words, half of which were repeated only once, immediately after initial presentation or belatedly, after presenting 4 to 6 different words: non-targets were classified into initial presenting words ($p = 0.45$), immediate repetition words ($p = 0.225$), and delayed repetition words ($p = 0.225$). A run consisted of a total of 120 exposures to stimuli. The order of the task was randomized across subjects. The data were compared to previous normal records (Matsuoka et al. 1999a, 1999b). Physical similarity, a likelihood questionnaire and DNA fingerprinting (Jack et al. 1995) were used to determine the zygosity of these twins. The unaffected twin has shown no psychiatric symp-

toms during the 5 years of follow-up to date.

The affected and unaffected twins were confirmed to be monozygotic based on physical similarity, a likelihood questionnaire and DNA fingerprinting. Table 1 and Fig. 1 show the results of visual NA and N400 potentials. Both twins showed delayed N400 latencies as compared with normal controls (z scores were 6.4 and 3.5 for pseudo-words, 10.8 and 6.6 for words) and both showed a lack of the repetition effect. The degree of delayed N400 latency was marked in the affected twin based on the z score comparison. Only the affected twin had a delayed NA latency as compared with the normal control.

TABLE 1. The latency and amplitude of cognitive components of brain potentials evoked by visual stimulation (visual event-related potentials; NA and N400).

Variables	Normal controls n = 10, mean (S.D.)	Unaffected twin	Affected twin
NA Potential			
Latency (msec)/amplitude (microV)			
Foreign letters	260 (22.9) / -9.0 (3.5)	252 / -11.5	**384** / -11.2
Pseudo-words	272 (23.9) / -16.4 (4.8)	270 / -11.4	**388** / -12.4
Words	270 (24.7) / -17.2 (4.4)	278 / -12.0	**352** / -9.2
N400 Potential			
Latency (msec)/amplitude (microV)			
Pseudo-words	412 (35.8) / -9.8 (3.6)	**536** / -11.5	**640** / -5.0
Words	420 (29.6) / -10.1 (2.8)	**614** / -10.8	**740** / -9.5
Repetition effects			
Subtraction of N400 potentials	-13.0 (4.6)	**-0.2**	**-3.2**

Visual stimulations consist of foreign letters, pseudo-words and words, i.e., unpronounceable foreign letters, two pronounceable but meaningless kana (Japanese phonograms) and two meaningful kana, respectively. The bold-faced values show differences as compared with normal controls based on z score comparison.

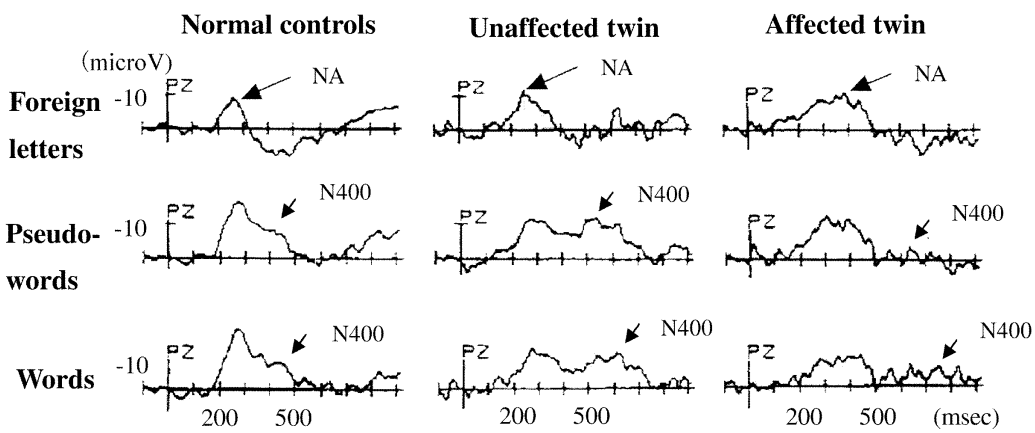

Fig. 1. Brain potential wave forms evoked by visual stimulations. NA and N400 show the peaks of the cognitive components of brain potential. Wave forms from middle parietal (Pz) area of the brain are shown. Visual stimulations consist of foreign letters, pseudo-words and words which are unpronounceable foreign letters, two pronounceable but meaningless kana (Japanese phonograms) and two meaningful kana, respectively.

Discussion

First, this twin pair satisfied the criteria for identical twins discordant for schizophrenia proposed by Suddath (1990). Furthermore, we avoided post-affected processes of schizophrenia in this case because the examinations were carried out soon after the onset of illness. The twins were monozygotic, assuring that abnormalities found in both twins were genetic in origin. Both twins lacked immediate repetition effects and had abnormally delayed N400 latencies. Lack of immediate repetition effects reflects a failure to use preceding word information and the twins showed almost the same results. It was possible that their impairments were independent of affectation. Lack of immediate repetition effects might also be attributable to genetic factors. On the other hand, the degree of delayed N400 latency was marked in the affected twin. Considering that N400 latency is thought to reflect semantic processing (Rugg 1995), the affected twin might have experienced accelerated deterioration after the disease onset. The delayed N400 latency might reflect acquired as well as genetic factors in schizophrenic subjects.

The abnormalities observed in the affected twin might have been derived solely from acquired vulnerabilities, triggering the onset of schizophrenia. The affected twin showed an abnormally delayed NA latency (z score: 3.3-5.2), while the unaffected twin had an apparently "normal" NA latency (z score: 0.1-0.4). As NA potential is reportedly associated with pattern recognition (Simson et al. 1985), only the affected twin had a deficit in pattern recognition. This pattern recognition deficit might be critical for the onset of schizophrenia. Therefore, the delayed NA latency might reflect non-genetic factors for schizophrenia development. However, we can offer no explanation for the non-genetic factors in these twins. A delayed NA latency is reportedly an index of relapse in schizophrenia (Matsuoka et al. 1999a). However, it might also serve as a critical index for the onset of schizophrenia.

In conclusion, this study demonstrates that 1) lack of repetition effects may reflect genetic vulnerability, 2) delayed N400 latency is possibly of both genetic and acquired origins and 3) delayed NA latency may reflect acquired vulnerability to schizophrenia development and may be a critical index for the onset of schizophrenia. These findings need to be reconfirmed in larger numbers of identical twins discordant for this affliction. Our examinations of one set of identical twins provide only preliminary data.

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